BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problems Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number: WO 92/09281
A61K 31/445	A2	(43) International Publication Date: 11 June 1992 (11.06.92)

(21) International Application Number: PCT/GB91/02062

(22) International Filing Date: 21 November 1991 (21.11.91)

(30) Priority data:

9025592.8	24 November 1990 (24.11.90)	GB
9025593.6	24 November 1990 (24.11.90)	GB
9025594.4	24 November 1990 (24.11.90)	GB
9025595.1	24 November 1990 (24.11.90)	GB

(71) Applicant *(for all designated States except US)*: BEECHAM GROUP PLC [GB/GB]; SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : JOHNSON, Anthony, Michael [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).

(74) Agent: RUSSELL, Brian, John; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US.

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: USE OF PAROXETINE FOR THE TREATMENT OF SENILE DEMENTIA, BULIMIA, MIGRAINE OR ANOREXIA

(57) Abstract

The use of paroxetine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of senile dementia.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MC	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU+	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE*	Germany	MC	Monaco	US	United States of America
DK	Denmark				

+ **Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.**

Use of paroxetine for the treatment of senile dementia, bulimia, migraine or anorexia.

The present invention relates to a method for the treatment of senile dementia, bulimia, migraine or anorexia and to a compound for use in such methods.

U.S. Patent 4 007 196 discloses the compound, (-)-trans-4-(4'-fluorophenyl)-3-(3'4'-methylenedioxy-phenoxymethyl)piperidine, and, in Example 2, a process by which it can be prepared. The compound, which is referred to herein by its common name, paroxetine, is described in the patent as an inhibitor of 5-hydroxytryptamine uptake and, therefore, is of use in the treatment of depression. The patent also mentions that paroxetine is useful in the treatment of Parkinson's disease.

It has now been discovered that paroxetine also has potential therapeutic utility for treating senile dementia, bulimia, migraine or anorexia.

Accordingly, the present invention provides a method for treating senile dementia, bulimia, migraine or anorexia in human or non-human animals, which method comprises administering an effective, non-toxic amount of paroxetine or a pharmaceutically acceptable salt thereof, to human or non-human animals suffering from senile dementia, bulimia, migraine or anorexia.

The present invention also provides the use of paroxetine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of senile dementia, bulimia, migraine or anorexia.

Examples of pharmaceutically acceptable salts of paroxetine are paroxetine hydrochloride, paroxetine hydrobromide, paroxetine acetate and paroxetine maleate. A preferred salt

is crystalline paroxetine hydrochloride hemi-hydrate.

A paroxetine medicament, for use in the treatment of senile dementia, bulimia, migraine or anorexia may be prepared by admixture of paroxetine or salt thereof with an appropriate carrier, which may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

Preferably, the medicament is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of senile dementia, bulimia, migraine or anorexia.

The suitable dosage range for paroxetine or a salt depends on the severity of the senile dementia, bulimia, migraine or anorexia and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

Paroxetine or a salt thereof may be formulated for administration by any route, and examples are oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may, if desired, be designed to give slow release of paroxetine.

The medicaments may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The medicaments, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycerine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid medicaments may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute paroxetine or a salt thereof throughout those medicaments employing large quantities of fillers. When the medicament is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The medicament may also be in the form of an ingestible capsule, for example of gelatin containing paroxetine or a salt thereof if desired with a carrier or other excipients.

Medicaments for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid medicaments may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated

edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

Paroxetine or a salt thereof may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the medicaments may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

As mentioned hereinbefore, the effective dose of paroxetine depends on the severity of the senile dementia, bulimia, migraine or anorexia, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 2 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 20, 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2,

3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of paroxetine and be administered in multiples, if desired, to give the preceding daily dose.

The present invention further provides a pharmaceutical composition for use in the treatment of senile dementia, bulimia, migraine or anorexia which comprises an effective amount of paroxetine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. Such compositions may be prepared in the manner as hereinbefore described.

The following example demonstrates a suitable pharmaceutical composition:

Example 1

The following were mixed together in a conventional manner and compressed into a tablet in a conventional manner.

22.88 mg	Paroxetine hydrochloride hemihydrate
244.12 mg	Dibasic calcium phosphate dihydrate
15.00 mg	Hydroxypropylmethyl cellulose 2910
15.00 mg	Sodium starch glycollate
3.00 mg	Magnesium Stearate
300.00 mg	Total tablet weight

Claims

1. The use of paroxetine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of senile dementia.

2. The use of paroxetine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of bulimia.

3. The use of paroxetine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of migraine.

4. The use of paroxetine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of anorexia.

5. A use according to any one of claims 1 to 4 wherein the medicament is adapted for oral administration.

6. A use according to any one of claims 1 to 4 wherein the medicament is adapted for parenteral administration.

7. A use according to any one of claims 1 to 4 wherein the medicament is in a unit dose from containing from 2 to 1000 mg of paroxetine or a pharmaceutically acceptable salt thereof.

8. A method for treating senile dementia in human or non-human animals, which method comprises administering an effective, non-toxic amount of paroxetine or a pharmaceutically acceptable salt thereof, to human or non-human animals suffering from senile dementia.

9. A method for treating bulimia in human or non-human animals, which method comprises administering an effective,

non-toxic amount of paroxetine or a pharmaceutically acceptable salt thereof, to human or non-human animals suffering from bulimia.

10. A method for treating migraine in human or non-human animals, which method comprises administering an effective, non-toxic amount of paroxetine or a pharmaceutically acceptable salt thereof, to human or non-human animals suffering from migraine.

11. A method for treating anorexia in human or non-human animals, which method comprises administering an effective, non-toxic amount of paroxetine or a pharmaceutically acceptable salt thereof, to human or non-human animals suffering from anorexia.

12. A method according to claim 8 in which the paroxetine or a pharmaceutically acceptable salt thereof is adapted for oral administration.

13. A method according to claim 8 in which the paroxetine or a pharmaceutically acceptable salt thereof is adapted for parenteral administration.

14. A method according to claim 8 in which the paroxetine or a pharmaceutically acceptable salt thereof is in a unit dose form containing from 2 to 1000 mg of paroxetine or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition for use in the treatment of senile demential which comprises an effective amount of paroxetine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

16. A pharmaceutical composition for use in the treatment of bulimia which comprises an effective amount of paroxetine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

17. A pharmaceutical composition for use in the treatment of migraine which comprises an effective amount of paroxetine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

18. A pharmaceutical composition for use in the treatment of anorexia which comprises an effective amount of paroxetine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

19. A pharmaceutical composition according to any one of claims 15 to 18 which is adapted for oral administration.

20. A pharmaceutical composition according to any one of claims 15 to 18 which is adapted for parenteral administration.

21. A pharmaceutical composition according to any one of claims 15 to 18 wherein the paroxetine or a pharmaceutically acceptable salt thereof is in a unit dose form containing from 2 to 1000 mg of paroxetine or a pharmaceutically acceptable salt thereof.